# The Comparison α-Blocker+M3 Selective Anti-Muscarinic Combined Therapy and α-Blocker Monotherapy

# α-Bloker Monoterapisi ile α-Bloker+M3 Selektif Antimuskarinik Kombine Tedavisinin Karşılaştırılması

Aşırı Aktif Mesane / Over Active Bladder

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**Özet**

Amaç: Benign prostat hiperplazisi ve eşlik eden aşırı aktif mesane semptomları olan erkek hastalarda alfa-blokör monoterapisi (doksazosin) ile alfa-blokör+M3 selektif antimuskarinik (doksazosin +darifenasin) kombinasyon tedavisinin etkinliği ve güvenilirliğinin karşılaştırılması. Gereç ve Yöntem: AÜSS ile başvuran yaşları 50 ve üzerinde olan 101 hasta çalışmaya alındı. Hastalar randomize olarak iki gruba ayrılarak bir gruba 4 mg doksazosin diğer gruba 4 mg doksazosin 7,5 mg darifenasin ile kombine edilerek tedavi başlandı. Hastalar EUA ve AUA'nın BPH kılavuzları doğrultusunda değerlendirildiler. Tedaviden sonraki 12.haftada hastalar tekrar değerlendirildi. Tüm hastaların; uluslar arası prostat semptom skorları (IPSS), IPSS yaşam kalitesi skorları (IPSS –QoL), maksimum idrar akım hızları (Qmax), ortalama idrar akım hızları (AFR), PVR idrar volümleri tedavi öncesi ve sonrası elde edildi. Bulgular: Kombinasyon tedavisi verilen grupta; total IPSS ve IPSS-QoL skorlarında monoterapi grubu ile karşılaştırıldığında ($p<0.01$) önemli derecede düşme oldu. Qmax ve AFR her iki grupta benzer bulundu ($p=0,732$). Kombine tedavi verilen grupta monoterapi grubuna göre önemli oranda ($p<0.01$) PVR artışı (>43 ml) gözlendi. Sonuç: BPH ve AAM'ye sekonder AÜSS olan erkeklerde alfa-blokör+m3 selektif antimuskarinik kombinasyon tedavisi semptomlar üzerine alfa blokör monoterapisine göre daha etkilidir. Ancak kombinasyon tedavisi önemli oranda PVR artışına neden olmaktadır.

**Anahtar Kelimeler**

Alfa Bloker; BPH; Aşırı Aktif Mesane; Kombine Tedavi

**Abstract**

Aim: Effectiveness and reliability comparison of alpha-blocker monotherapy (doksazosin) and combined alpha-blocker+M3 selective antimuscarinic (doksazosin+darifenacin) treatments on male patients with Benign prostate hyperplasia and accompanying OAB (overactive bladder) symptoms. Material and Method: 101 patients with ages 50 and above who had LUTS (Lower urinary tract symptoms) complaints were included in the study. Patients were randomly organized into two groups. One group had treatment with 4mg doksazosin, the other group had 4mg doksazosin combined with 7.5mg darifenacin. Patients were evaluated in accordance with BPH manuals of EUA (European Urology Association) and AUA (American Urology Association). Patients were re-evaluated on 12th week after the treatment. International prostate symptom scores (IPSS), IPSS quality of life scores (IPSS-QoL), maximum urine flow rate (Qmax), average urine flow rates (AFR) and PVR (Post Voiding Residual Volume) data were obtained before and after the treatment from all patients. Results: Patients who received combined treatment had experienced considerable drop ($p<0.01$) in total IPSS and IPSS-QoL scores compared to monotherapy group. Qmax and and AFR data were found nearly equal ($p=0.732$). Considerable increase ($p<0.01$) in PVR (>43ml) in combined treatment group was observed. Discussion: Alpha-blocker+M3 selective antimuscarinic combined treatment is more effective than alpha-blocker monotherapy on male patients with LUTS secondary to BPH and OAB. However combined treatment causes considerable increase in PVR.

**Keywords**

Alpha Blocker; BPH; OAB; Combined Treatment

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## Introduction

Benign prostatic hyperplasia (BPH) causes prostatic enlargement, which may result in bladder outlet obstruction (BOO) [1]. Lower urinary tract symptoms (LUTS) in men are often attributed to prostatic enlargement and BOO [2] which increase dramatically in prevalence over 40 years of age [1–4].

Overactive bladder (OAB) is a syndrome of spectrum LUTS defined by the International Continence Society (ICS) as urgency, with or without urge urinary incontinence, usually with increased frequency and nocturia [5]. OAB symptoms are as frequent as BPH symptoms, increasing in prevalence among men over 40 years of age [4]. Urodynamic studies about the subject report that only 48% to 68% of men with LUTS have BOO [6,7]. Thus, LUTS in men may result from either prostatic enlargement or other conditions leading to OAB.

LUTS in men are commonly treated with agents that target the prostate and/or bladder outlet, such as α-adrenergic antagonists and 5α-reductase inhibitors [8]. These agents may have limited efficacy over OAB symptoms that may originate from bladder dysfunction, especially in forms secondary to BOO [8]. On the other hand, antimuscarinics are first-line pharmacotherapy for OAB [6] and are effective in men [8–12]. However, antimuscarinics are not widely prescribed for men, because of the reason that clinicians often associate male LUTS with prostatic pathology rather than bladder dysfunction and/or with fear of acute urinary retention (AUR) [8,13]. Several studies have shown that concerns about increased incidence of AUR may be variable [2].

The mainstay of OAB pharmacotherapy is the use of antimuscarinics to inhibit inappropriate bladder contractions that give rise to OAB symptoms [1]. Darifenacin is a novel antimuscarinic agent developed for the treatment of OAB and it shows up to 59-fold selectivity for M3 receptors when compared to other muscarinic receptor subtypes in vitro [11]. The clinical effectiveness of darifenacin in the treatment of the general OAB patients has been demonstrated in several large phase III studies [12,14,15,16]. Despite this, there is no data about the efficacy of combination therapy of darifenacin and alpha adrenergic drugs in men with LUTS including OAB. Thus, the aim of the present study was to evaluate efficacy and safety of darifenacin-doksazosin combination and compare with alpha adrenergic antagonists in men with LUTS including OAB.

## Material and Method

Eligible men were aged > 50 years with a total International Prostate Symptom Score (IPSS) >12, bladder diary-documented frequency (>8 micturitions per 24 h) and urgency (>3 episodes per 24 h) with or without urgency urinary incontinence (UUI) and at least "some moderate problems" related to their bladder condition reported on the Patient Perception of Bladder Condition at baseline [18]. Exclusion criteria were as follow: Subjects with significant BOO (post void residual volume [PVR] >150mL, maximum urinary flow rate [Qmax] <5mL/s), the patients who had previous prostatic surgery, and with serum PSA levels > 10 ng /mL, the patients with bladder stone, diverticula and urinary tract infections, the patients with urethral stricture and neurogenic bladder or diabetes mellitus. The patients who were treated with any α-adrenergic antagonist and antimuscarinic agents or diuretic medicine were also excluded from the study. The patients with serum PSA levels between 4 and 10 ng/mL were undergone transrectal ultrasound guided prostatic biopsy for excluding carcinoma and the patients who prostatic carcinoma diagnosed histopathologically were not included into the study. Subjects were randomized to receive double-blind treatment with doxazocin (4mg) or doxazosin (4mg) + darifenacin (7.5 mg) for 12 weeks. Qmax and PVR were determined at baseline and at the end of 12 weeks using a flowmeter and ultrasound, respectively. Serum PSA levels were also measured at baseline and at the end of treatment protocol.

### *Statistical Analysis*

Analysis of efficacy was measured from data of all study participants who received at least one method of randomized medication and had both a baseline (where applicable) and post-baseline efficacy assessment (full analysis set) investigation. Mean changes from baseline at the end of the treatment protocol at 12 weeks IPSS total, Qmax and PVR were compared between groups by using the Wilcoxon rank-sum test, stratified by study. A non-parametric analysis was performed because of the abnormal distribution of the outcome data.

## Results

The study population comprised of 101 patients with LUTS secondary to BPH whom were aged >50 years and were the subject of this study. Demographics and baseline clinical characteristics were broadly similar across treatment groups (Table 1).

IPSS scores were significantly improved in doxazosin + darifenacin receiving group when compared to doxazocin group. On the other hand, IPSS storage and voiding scores were also significantly improved in men who received doxazosin+darifenacin treatment (p<0.01). QoL (Quality of Life) scores were improved significantly after the treatment of doxazocin+ darifenacin (p<0.01) (Table 2).

The incidence of acute urinary retention (AUR) was low in both groups. Statistically significant changes in PVR or Qmax were

Table 1. Demographics and baseline clinical characteristics of the treatment groups.

| | Doxazocin (n=50) | Darifenacin+Doxazocin (n=51) |
|---|---|---|
| Mean age | 63.76 | 65 |
| Total | 16.04 ± 3.75 | 16.6 ± 4.37 |
| Storage | 6.3 ± 2.9 | 6.4 ± 2.6 |
| Voiding | 10.3± 4.5 | 10.5 ± 4.5 |
| QoL | 3.2 | 3.5 |
| Qmax mL/s | 12.02 ± 5.44 | 13.03 ± 4.67 |
| PVR mL | 63.1 ± 5.3 | 45.49 ± 3.9 |

Table 2. Demographics and baseline clinical characteristics of the groups after the treatment of doxazocin+ darifenacin (p<0.01).

| | Doxazocin (n=50) | Doxazocin +Darifenacin (n=51) |
|---|---|---|
| Total | 9.18 | 6.27 |
| Storage | 5.21 | 2.8 |
| Voiding | 4.0 | 3.4 |
| QoL | 2.2 | 1.7 |
| Qmax mL/s | 16.6 | 16.8 |
| PVR mL | 43.8 | 33.9 |

Table 3. The most seen side effects of combined therapy (Doxazocin+Darifenacin)

| Side Effects | Doxazocin ( N=50 ) | Doxazocin+Darifenacin ( N=51 ) |
|---|---|---|
| Xerostomia | 0 | 10 ( %19.6) |
| Constipation | 1 (% 2) | 13 ( %25.4) |
| Dyspepsia | 2 (%4) | 3 ( %5.88) |
| Headache | 3 (% 6) | 2 ( %3.92) |
| Neurological Symptoms | 1 (%2 ) | 1 (%1.98) |
| Postural Hypotension | 13 (%26) | 9 (%17.64) |

observed in both groups at the end of 12 weeks (Table 2). The treatment was well tolerated in both groups. The most common adverse events were dry mouth, constipation and dyspepsia (Table 3), which were typically mild and none of them caused treatment discontinuation.

**Discussion**

It's well known that some anticholinergic agents have been associated with high intolerance and safety issues that may make them inappropriate for use in older patients [3,4]. Such problems can be linked to the non-selective actions of some anti-muscarinic agents for the muscarinic M3 receptors, which are primarily responsible for mediating human bladder contraction [13]. In addition to this, these agents block a range of other muscarinic receptor subtypes that are widely distributed through out the body [9], giving rise to a diverse profile of adverse effects. Potential problems include cognitive impairment (e.g. memory and attention) and cardiac side effects (such as tachycardia) primarily through blockade of M1 and M2 receptors, respectively [2]. Although such problems would not be of concern for younger age group, older patients may be at particular risk as a result of their greater likelihood to exhibit comorbidities. Because of these reasons, an aging population needs a new line OAB medication that is efficacious, well-tolerated and safe in this age group.

Muscarinic receptors in bladder smooth muscle play an important role in mediating bladder contraction which is widely believed to be the primary therapeutic site of action of antimuscarinics [9]. Bladder Outlet Obstruction (BOO) which is associated with BPH and prostatic enlargement may or may not be accompanied by secondary bladder conditions [8,13] and their response to treatment may vary. Men with LUTS due to primary bladder conditions may respond favorably to antimuscarinic therapy alone, whereas those with LUTS due to prostatic enlargement with concomitant or secondary bladder dysfunction may require antimuscarinic and a-blocker therapy to achieve comparable benefits. Effective and safe antimuscarinic treatment of older patients with OAB and BPH represents a major therapeutic challenge to healthcare professionals, [8] because of tolerability and safety concerns in older individuals [5,6]. The availability of darifenacin, a novel antimuscarinic with an M3 selective profile that may limit the risks associated with blockade of other receptor subtypes [2], represents a promising new alternative for the treatment of older patients with OAB. In view of its selectivity for muscarinic M3 receptors, darifenacin is expected to minimize the risk of side effects related to blockade of non-M3 receptor subtypes such as M1-mediated cognitive impairment [2]. This is of particular importance in older patients who may be more susceptible to cognitive impairment and nervous system side effects. Such patients are also at increased risk of neurological symptoms resulting from increased blood–brain barrier permeability associated with advancing age [17] or conditions such as Alzheimer's disease [18], multiple sclerosis [19] and diabetes [20]. M3 receptor selectivity is also expected to decrease the risk of cardiac (primarily M2-receptor mediated) side effects [2].

This interpretation is supported by the report with better results in men with only BOO (79%) when compared with men with both BOO and OAB (35%) in which, IPSS voiding scores (>3 points) after 3 months of treatment with doxazosin alone taken into consideration [21]. Among men who did not respond to doxazosin monotherapy, 73% of the patients with BOO and DO, and 38% of patients with only BOO, responded well to darifenacin-doxazosin combination therapy.

Darifenacin+tamsulosin was efficacious in men with BPH. Compared with the placebo and doxazocin group, subjects in the darifenacin + doxazosin group showed significant improvements in total and subscale IPSS scores. Notably, darifenacin together with doxazosin was well tolerated. No evidence of AUR and no clinically significant changes in PVR or Qmax were observed in any treatment group with BPH. Main reason that antimuscarinic therapy may be well tolerated with a low rate of AUR could be the reduction of the number of muscarinic receptors in the male detrusor with aging [22].

It is notable that all subjects in the current study met symptom-entry criteria for both OAB and prostatic enlargement trials. Thus, it is likely that men with LUTS will benefit most from therapeutic interventions that are individually adjusted for maximum efficacy, rather than therapy based on generic treatment algorithms. Obviously, urodynamic measurements may help to guide the choice of therapy for individual patients. The results of this study should be interpreted within the context of its limitations. This study did not assess impact of age, body mass index, duration of LUTS, and Qmax on treatment responsiveness. Future analyses will evaluate the impact of these factors and whether there are differences in long-term impact (eg, prevention of symptom progression and need for invasive therapy) of treatment modalities.

In conclusion, among men who met symptom-entry criteria for prostate enlargement and OAB trials, therapy with darifenacin+ doxazocin effectively improved LUTS, including OAB symptoms in this population. Men with moderate to severe LUTS including OAB with BPH may require therapy with an alpha-receptor antagonist and darifenacin to achieve treatment benefit.

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